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ARTICLE

Multicenter Surveillance of Invasive Meningococcal Infections in Children

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ABSTRACT

OBJECTIVES. Meningococcal disease continues to result in substantial morbidity and mortality in children, but there is limited recent surveillance information regarding serogroup distribution and outcome in children in the United States. The objective of this study was to collect demographic, clinical, laboratory, and outcome information for infants and children who had *Neisseria meningitidis* infections of various serogroups and were cared for in 10 pediatric hospitals.

METHODS. Investigators at each of the participating hospitals identified children with meningococcal infections and collected demographic and clinical information using a standard data form. Meningococcal isolates were sent to a central laboratory for serogrouping by slide agglutination and penicillin susceptibility.

RESULTS. From January 1, 2001, through March 15, 2005, 159 episodes of systemic meningococcal infections were detected. The greatest numbers of children were younger than 12 months (n = 41) or were 12 to 24 months of age (n = 22). Meningitis was the most common clinical manifestation of disease accounting for 112 (70%) cases; 43 (27%) children had bacteremia only. Children who were younger than 5 years (17 of 102) were significantly less likely to require mechanical ventilation than children who were 5 to 10 years of age (12 of 24) or children who were older than 10 years (13 of 33). Overall, 55 (44%) isolates were serogroup B, 32 (26%) were serogroup C, and 27 (22%) were serogroup Y. All but 1 isolate (intermediate) were susceptible to penicillin. The overall mortality rate was 8% (13 of 159) but was greater for children who were ≥11 years of age (7 [21.2%] of 33) than for children who were younger than 11 years (6 [4.8%] of 126). Unilateral or bilateral hearing loss occurred in 14 (12.5%) of 112 children with meningitis.

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Key Words
Neisseria meningitidis, surveillance, meningitis

Abbreviations
CSF—cerebrospinal fluid
MIC—minimum inhibitory concentration
rBPI$_{21}$—recombinant bactericidal permeability increasing protein

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CONCLUSIONS. The morbidity and the mortality of meningococcal infections are substantial. With the recent licensure of meningococcal conjugate vaccines, our baseline trends in meningococcal disease can be compared with those seen after widespread vaccination to assess the success of routine immunization.

EACH YEAR ~1400 to 2800 cases of meningococcal disease occur in the United States; the most current estimate is that 2240 cases occurred in 2001.[1] Children who are younger than 1 year have the highest age-specific incidence, and another slight peak occurs starting at adolescence.[1,2] There has been only a single general report describing invasive meningococcal infections in children in the United States since the mid-1990s.[3] Other publications have presented single-site or -city/county data ranging as far back as 1981 through 1997.[4–6] The most current information, reported from Arkansas in 2002, covered a 12-year span that ended in 2000.[3]

In anticipation of the licensure and routine use of conjugate meningococcal vaccines in the United States, 10 children's hospitals organized a meningococcal surveillance network to monitor invasive meningococcal infections in children. This report describes 51.5 consecutive months of surveillance that immediately preceded the date on which the tetravalent meningococcal conjugate vaccine (Menactra; Sanofi Pasteur, Swiftwater, PA) first was available for administration (March 15, 2005).

METHODS

The US Multicenter Meningococcal Surveillance Study Group is composed of investigators from 10 children's hospitals in the United States. Investigators identified all children who were seen at their institution with systemic infections that were caused by *Neisseria meningitidis*. Systemic infections were defined by isolation of the organism from a sterile body site, such as cerebrospinal fluid (CSF), blood, pleural fluid, or joint fluid. Meningococcal meningitis was defined as either a CSF culture or rapid antigen test (1 child with CSF white blood cell count = 320/mm^3) that was positive for *N meningitidis* or a CSF pleocytosis (>5 white blood cells per mm^3) plus a blood culture positive for *N meningitidis*. Bacteremia was considered acute, fulminant, occult, or chronic at the discretion of the investigator. Pneumonia was defined as a positive blood culture in a child with a chest radiograph consistent with pneumonia. The study period was from January 1, 2001, through March 15, 2005. A standard data form that included demographic and clinical information and outcome was completed retrospectively for each infectious episode. Patient information was entered into a computerized database that was maintained at Baylor College of Medicine. Hypotension for age on admission was as defined using the Glasgow meningococcal septicemia prognostic score.[7] Fever was defined as a temperature that exceeded 100.4°F regardless of site. The institutional review board at each center approved this study.

Meningococcal isolates were identified by standard methods in the microbiology laboratories of each hospital and were sent to a central laboratory (Infectious Disease Research Laboratory, Texas Children's Hospital, Houston, TX), where they were stored frozen in Dorset egg medium. Isolates were serogrouped (A, B, C, Y, or W-135) by slide agglutination using antisera from Difco (Detroit, MI). Serogroup determination by the local or state health departments was used (n = 8) when isolates were not available for retesting in Houston. Serogroup was not determined for 35 isolates. Antimicrobial susceptibilities were performed by microbroth dilution using cation-adjusted Mueller-Hinton broth with 3% lysed horse blood. Susceptibility categories were susceptible (penicillin minimum inhibitory concentration [MIC]: ≤0.06 μg/mL; ceftriaxone MIC: ≤0.12 μg/mL), intermediate (penicillin MIC: 0.12–0.25 μg/mL; ceftriaxone MIC not defined), or resistant (penicillin MIC ≥0.5 μg/mL; ceftriaxone MIC not defined) as defined by the 2005 Committee for Clinical Laboratory Standards Institute.[8] Dichotomous variables were assessed by χ^2, Fisher's exact test, or log-likelihood using True Epistat (Epistat Σ Services, Richardson, TX).

RESULTS

During the 51.5-month surveillance period, 159 episodes of systemic meningococcal infections occurred. Almost all infections were confirmed by culture. The age distribution of the patients is shown in Fig 1. The greatest numbers of children were younger than 12 months (n = 41) followed by 12 to 24 months of age (n = 22). Two (1.3%) patients were ≤30 days of age (16 days old with meningitis; 29 days old with bacteremia). Sixty-six percent of children were ≤5 years of age. The numbers of children decreased with age until 8 years of age, when

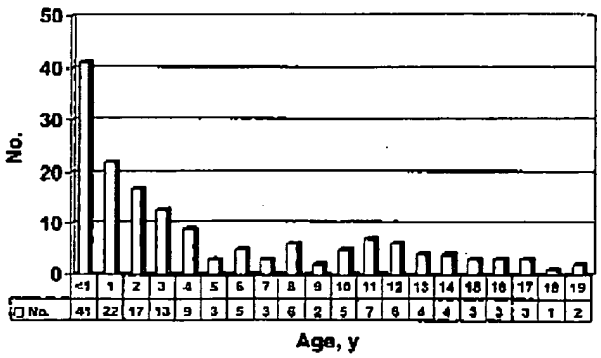

FIGURE 1
Age distribution of children with invasive meningococcal infection.

a slight increase occurred, peaked at 11 years, and declining again through 16 years of age. Ninety-six (60%) children were male. Eighty-six patients were white, 30 were Hispanic, 25 were black, and 10 were other; in 8 cases, the race/ethnicity was unknown.

An underlying condition was present in only 9 (5.6%) patients (complement deficiency detected as a result of the meningococcal infection [2], sickle cell disease [2], congenital hydrocephalus [1], ventricular septal defect [1], lung transplant for cystic fibrosis [1], autoimmune hepatitis [1], and prematurity [1]). One patient (19 years of age) received the meningococcal polysaccharide vaccine 1.5 years before onset of this infection (serogroup B). Three secondary cases of meningococcal disease were identified in the daughter of a baby-sitter, a household contact, and a patient in close proximity in the ICU.

Focus of Infection

Meningitis was the most common manifestation of invasive meningococcal infection, accounting for 112 (70%) cases. (Table 1) Forty-three (27%) children had bacteremia alone (acute: 30; fulminant: 7; and occult: 6). Four children had pneumonia; 1 fatal case was complicated by empyema. One patient had septic arthritis. Selected clinical and laboratory features, including CSF results, based on age are shown in Tables 2 and 3. Children who were ≤5 years of age were significantly more likely to be neutropenic (absolute neutrophil plus band count ≤1500/mm^3) on admission than older children ($P = .007$).

Overall, 42 (26%) children required mechanical ventilation and 52 (33%) received vasopressors. Children who were younger than 5 years (17 of 102) were significantly less likely ($P < .001$) to require mechanical ventilation than children who were 5 to 10 years of age (12 of 24) or children who were older than 10 years (13 of 33). The mean duration of fever after antibiotics were initiated was 1.9 days (range: 0–14 days); 90% of patients were afebrile by day 5.

Twenty-nine children received dexamethasone, and in those with meningitis, dexamethasone was administered to 22 (20%) of 112. Protein C was administered to 9 children; 1 received recombinant bactericidal permeability increasing protein (rBPI$_{21}$).

TABLE 1 Distribution of Ages and Site of Infection for Children With Meningococcal Infections

Diagnosis	≤5 y	6–10 y	>10 y
Meningitis	72	15	25
Bacteremia alone	32	4	6
Other[a]	1	2	2

[a] Septic arthritis and pneumonia.

TABLE 2 Selected Clinical and Laboratory Features in Children With Meningococcal Infections According to Age at Admission to the Hospital

Features	≤5 y (n = 105)	6–10 y (n = 21)	>10 y (n = 33)
Petechiae	57[a]	13	17
Purpura	36	11	13
Hypotension	13	0	3
Platelet count <100 000/mm^3	5	1	3
Absolute neutrophil count <1500/mm^3	8[b]	0	0

[a] Absolute number.
[b] $P = .007$ by log-likelihood test.

TABLE 3 CSF results in 109 Children With Meningococcal Meningitis

CSF Parameter	≤5 y (n = 72)	6–10 y (n = 15)	>10 y (n = 25)
White blood cells, per mm^3			
Mean	3504	7209	6782
Median	1400	3012	4450
Range	1–18 250	751–50 000	6–28 500
% PMNs			
Mean ± SD	81 ± 21	90 ± 13	86 ± 22
Median	87	94	91
Range	4–100	50–99	1–109
Glucose, mg/dL			
Mean	53	34	35
Median	38	42	36
Range	<1–699	1–89	1–73
Protein, mg/dL			
Mean	204	425	381
Median	144	414	259
Range	11–871	88–924	20–1379
Gram-stain positive			
n (%)	36 (57)	11 (73)	17 (74)
No. of patients	9[a]	0	2[a]

PMNs indicates polymorphonuclear neutrophils.
[a] Number of patients with results not available.

Serogroups and Antibiotic Susceptibility

The distribution of meningococcal serogroups is shown in Table 4. Overall, 55 (44%) isolates were serogroup B, 32 (26%) were serogroup C, and 27 (22%) were serogroup Y. Serogroups A and W-135 accounted for 1 isolate each, and 8 isolates could not be serogrouped. Thirty-five isolates were unavailable for typing. There were

TABLE 4 Distribution of Meningococcal Serogroups and Age of Children With Infections Caused by *N meningitidis*

Age, y	Meningococcal Serogroups					Nontypeable
	B	C	Y	W135	A	
<1	19	4	9	0	1	4
1–5	20	15	10	0	0	4
6–10	6	5	3	0	0	0
>10	10	8	5	1	0	0
Total	55	32	27	1	1	8

Serogroup was unknown for 4, 15, 7, and 9 isolates from children <1, 1 to 5, 6 to 10, and >10 years of age, respectfully.

no differences in the distribution of serogroups for the age categories shown in Table 4 or for the site of infection. The isolates from the 3 children with pneumonia were serogroup C for 2 and unknown for 1.

The distribution of penicillin MICs for the available isolates was 0.008 μg/mL in 45, 0.015 μg/mL in 26, 0.03 μg/mL in 4, and 0.06 μg/mL in 2. The MIC for 1 isolate was 0.125 μg/mL, which was defined as intermediate susceptibility. All isolates were susceptible to ceftriaxone.

Outcome

The mortality rate for all patients with invasive infections was 8% (13 of 159). The mortality rate was greater for children who were ≥11 years of age (7 [21.2%] of 33) than for children who were younger than 11 years (6 of 126 [4.8%]; relative risk: 3.0; 95% confidence interval: 1.6–5.6; $P < .001$). Mortality in the 3 age groups of ≤5 years, 6 to 10 years, and >10 years was 4 (3.8%) of 105, 2 (9.5%) of 21, and 7 (21.2%) of 33, respectively ($P = .01$). Of the 13 patients who died, 9 had meningitis, including 1 that was associated with fulminant bacteremia, and 4 had fulminant bacteremia alone. There was no significant difference in mortality rates for children with meningitis (9 of 112) versus those with bacteremia alone (4 of 43). The serogroups of the isolates from the children who died were B (5), C (3), Y (1), nontypeable (1), and unknown (3). There was no association between mortality and serogroup. Four children died on the day of admission, 3 on day 1, 4 on day 2, and 1 each on days 8 and 10.

Sequelae that were observed in the hospital are shown in Table 5. Hearing loss occurred in 14 children (all ≤10 years of age; 8 ≤2 years of age), or 12.5% of those with meningitis. Skin necrosis ($n = 13$; 9 ≤4 years of age) with some requirements for grafting was the second most common sequela. Two children had amputations. Three children had vasculitis, and 1 had pericarditis, all considered manifestations of immune complex disease by the site investigator.

TABLE 5 Sequelae of Meningococcal Infection in 146 Surviving Children During or After Hospitalization

Sequelae	*n*
Amputation	1[a], 1[b]
Skin necrosis	14
Skin graft	4
Seizures after admission	9
Unilateral deafness	6
Bilateral deafness	8
Ataxia	4
Hemiplegia	3

[a] Four extremities.
[b] Toes.

DISCUSSION

In anticipation of the licensure of a meningococcal protein conjugate vaccine in the United States, a 10-center pediatric surveillance study was organized to monitor meningococcal infections in children. To our knowledge, these findings represent the most up-to-date information for meningococcal disease in children in the United States.

During the 51.5 months of surveillance, 159 invasive cases were identified. Meningococcal disease remains most common in children who are younger than 2 years, but we also noted an increase in the number of patients beginning at 8 years of age, similar to previous reports.[9] Two infants who were younger than 1 month were identified, accounting for 5% of 41 cases in the first year of life. Shepard et al[10] reported that the rate of neonatal meningococcal infection in the United States was similar to that in 6- to 23-month-old children.

Unlike invasive pneumococcal infections, in which ~25% of children have an underlying medical condition,[11] only 5.7% of the patients with meningococcal disease had some underlying illness. These findings are consistent with those of Stovall and Schutze.[3] Most patients had meningitis in this study, as has been the case for other pediatric studies.[3,6] However, we did not find any difference in the distribution of the site of infection on the basis of age. Mechanical ventilation and the administration of vasopressors commonly were required; mechanical ventilation was required significantly ($P < .004$) more often in older children.

Skin necrosis occurred in 9.4% (15 of 159) of the children with invasive infections; 4 (2.6%) required skin grafts. Two children had amputations (1 lost 4 limbs, and 1 had toe losses). These rates are very similar to those found by earlier investigations. Unilateral or bilateral hearing loss occurred in 14 (12.5%) of 112 patients with meningitis, a rate very similar to reports from almost 25 years ago.[12]

There was a relatively even distribution of serogroups B, C, and Y in children in this study, as has been the case for patients in the United States since 1996.[1,3,13–15] The current meningococcal conjugate vaccine licensed in the United States contains polysaccharides for serogroups A, C, Y, and W-135 and would provide protection against more than half of the isolates that were recovered in this study. It is of interest that the only isolates that could not be serogrouped were from children who were younger than 5 years.

In 2005, the Clinical Laboratories Standards Institute developed breakpoints for interpreting MICs for isolates of *N meningitidis*.[8] Susceptibility to penicillin is decreasing among meningococcal isolates in several areas of the world.[16] However, only 1 penicillin-intermediate and no penicillin-resistant meningococcal isolates were encountered in this study.

The overall mortality of 8% in our study was very similar to that reported by others.[4,3,6] However, we did

find that mortality was greater for older children, something that was not addressed in these other studies. Wong et al[17] from Los Angeles reported that the mean age of 10 children with fatal meningococcal infection was 17.1 vs 33.2 months for the 90 nonfatal cases ($P > .05$).

Although surprising, these mortality rates are not much different from those reported ≥20 years ago despite the medical expertise and technology that are available in modern PICUs.[14] Novel adjunctive measures such as $rBPI_{21}$ or recombinant human activated protein C did not influence mortality, although $rBPI_{21}$ was associated with fewer complications of meningococcal disease in a randomized trial.[7,19] A recent randomized trial of recombinant human activated protein C in pediatric sepsis was stopped early because the improvement over placebo in the primary end point (composite time to complete organ resolution over 14 days) was not likely to be demonstrated and there were safety concerns related to increased intracranial bleeding in the activated protein C arm.[20] Therefore, the importance of preventing meningococcal disease is emphasized further.

However, because cases are limited to patients who were seen at children's hospitals, our findings might be biased. The number of patients who were older than 15 years may not be reflective of the overall burden of disease in this age group because these patients are not as likely to be referred to a children's hospital than are younger children. In addition, the severity of disease may be overestimated if children with relatively mild infections are not referred to tertiary children's hospitals.

In other countries, where the serogroup C conjugate meningococcal vaccine has been used routinely in infants for several years, the number of serogroup C cases has declined almost 80% among immunized children, and substantial herd protection has been observed for unimmunized children.[21,22] As the age for which the conjugate meningococcal vaccines is recommended declines in the United States, the total number of invasive meningococcal infections and related mortality should decline considerably. However, the absence of an effective serogroup B meningococcal component will dampen the impact of vaccine efficacy. Therefore, continued surveillance of invasive meningococcal infections in children will be critical to assess the success of routine immunization of children with conjugate meningococcal vaccines as well as to monitor for possible serogroup replacement, which has not been an issue so far in the United Kingdom and other countries where the conjugate meningococcal vaccine has been provided routinely to children for many years.

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